Pigmentation

Introduction

Skin pigmentation is regulated by **melanocytes**. Melanocytes make **melanin**, the pigment of skin. Melanocytes donate melanin to keratinocytes in structures called melanosomes. Keratinocytes want to make room for more keratin, so they degrade their organelles and their own nuclei as they become more and more terminally differentiated into corneocytes. Keratinocytes use that melanin to protect the nuclei of the stratum basale from UV radiation. But keratinocytes also need melanin to protect their nucleus from UV radiation. As a keratinocyte becomes terminally differentiated into a corneocyte, as the cell reaches higher and higher in the epithelium, farther and farther away from the stratum basale, the cell gets rid of those melanosomes to make room for keratin.

Melanocytes are derived from the **neural crest cells** (the rest of the skin is made of ectoderm). Melanocytes are staggered along the **stratum basale** of the epidermis. They burrow their way underneath the basal cells, between the basal cells and the basement membrane. There melanocytes **synthesize pigment** (melanin) from **tyrosine** in lysosome-like organelles called **melanosomes**. The melanosomes are lipid double bilayer organelles that contain pigment. The melanocytes have long dendritic projections that reach into the stratum basale. These dendritic projections are lipid double bilayers. The cells these dendritic projections butt up against have cell membranes made of a lipid double bilayer. The melanosome is transferred from the melanocyte into the keratinocyte through fusion of the membranes.

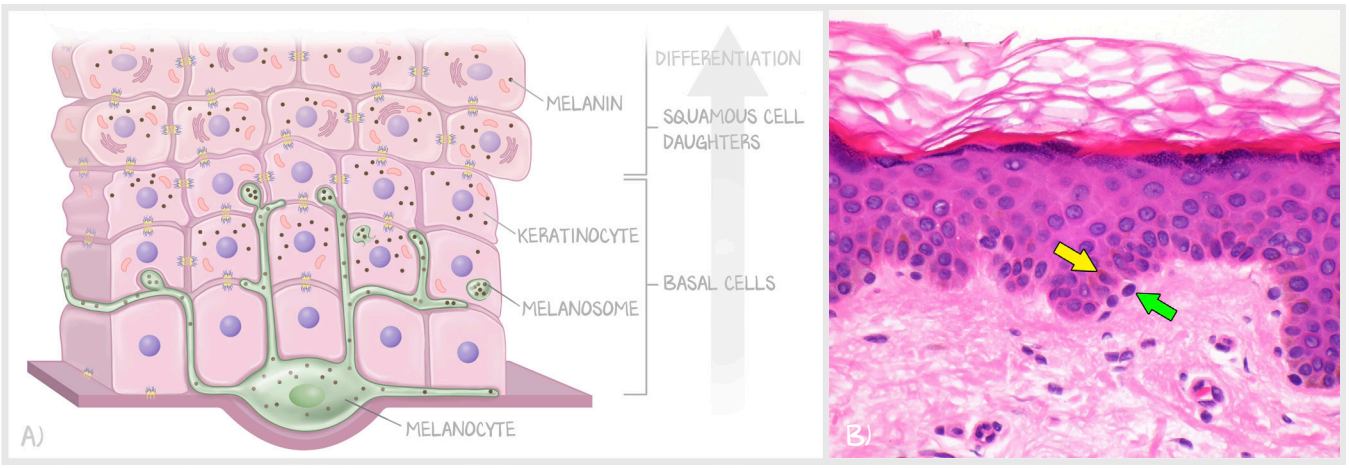


Figure 5.1: Melanocytes
(a) Melanocytes deposit melanin, via melanosomes, into cells of the stratum basale. They divide, and the daughter takes some melanosomes with it. (b) Melanocytes produce melanin and then transfer it to adjacent basal keratinocytes which store the melanin. Thus, the cells with brown melanin pigment in their cytoplasm along the stratum basale are actually basal keratinocytes (yellow arrows) rather than melanocytes. The melanocytes (green arrows) have slightly smaller and darker nuclei and have pale gray (not brown) cytoplasm.

We provide an in-depth discussion of pigmentation in general, then transition into the disorders of hypopigmentation and hyperpigmentation.

Skin and the Sun

This section is long. It has a nonlinear story but includes information necessary for understanding pigment, the purpose of pigment, and how skin cancers occur. While we really only need the information for pigment in this lesson, UV radiation, pigment, and proliferation are intricately related.

In addition, while we have put moles in this lesson and melanoma in another, there is an overt overlap in the pathogenesis, thus we discuss how they are related in this section.

Skin has both a color and a darkness, called tone. The number of melanocytes is about the same in all humans, regardless of their skin color. Melanocytes make a genetically predetermined amount of melanin, deliver keratinocytes a genetically predetermined number of melanosomes, and keratinocytes degrade melanin/melanosomes at a genetically predetermined rate. **Without pigment**, human skin and hair is **white**. A person's default skin **color** is determined by the relative amounts of melanin—pheomelanin (red/yellow) and eumelanin (brown/black)—that are synthesized. How **dark** a person's skin is by default depends on both the **rate of melanosome synthesis and transfer** AND the **rate of melanosome degradation**. The melanosomes in the keratinocytes of light-skinned individuals are fully degraded as those keratinocytes terminally differentiate into corneocytes. The keratinocytes of dark-skinned individuals do not fully degrade their melanosomes, and corneocytes desquamate with melanosomes in them.

The purpose of pigment is to protect the DNA of the stratum basale, protect the DNA of the basal stem cells and melanocytes. Pigment is transferred into the keratinocytes. They serve as the barrier between the UV radiation and those stem cells at the base of the epidermis. **UV radiation damages DNA.** Corneocytes have no DNA, so are unaffected. The stratum corneum remains intact when UV radiation exposure occurs. Keratinocytes in the stratum spinosum accumulate DNA damage. They have intact transcriptionally active nuclei. With accumulation of DNA damage, they undergo apoptosis and release vasoactive compounds that cause edema and capillary dilation. This is why **sunburns are red**. The more UV radiation there is, or the longer it goes on for, the deeper in the epidermis the keratinocytes will be affected. Minor sunburns are red; serious sunburns blister. They blister because enough keratinocytes in the stratum spinosum apoptose that the epidermis effectively undergoes acantholysis, while the stratum corneum sustains the dome of the blister. With loss of the keratinocytes that protect them, **basal cells must proliferate** to rebuild the keratinocyte shield**.** This is the effect of **too much UV radiation acutely**. Basal cell proliferation increases the opportunity for mutations. The UV damage that killed the keratinocytes also damages the basal cell, which can also induce mutations. Thus, the risk of basal cell and squamous cell carcinomas, the skin cancers of stem cells, increases with **sunburns**. That is why we thought it was sunburns that mattered most.

Now we know that risk is associated with **simple sun exposure**. Here's why.

Some UV radiation reaches the stem cells. They notice (the mechanism is not important), and seek to shield themselves from that radiation. They can do that with a taller epidermis (a higher column of keratinocytes containing pigment) or by every keratinocyte simply having more pigment. In the case where there isn't apoptosis, where a sunburn does not occur, the basal cells increase transcription of the POMC gene. One product of this gene is **α-MSH** (melanocyte-stimulating hormone, MSH). MSH is released from the basal cells to the nearby melanocytes, which stimulates the **MC1-receptor**, the downstream effect of which is an increased transcription for eumelanin and melanosome proteins. **MSH increases melanosome synthesis.** More melanosomes and more eumelanin darken the skin. This explains the mechanism of **tanning**, and also explains why the skin darkens for days after the sun exposure—upregulation of transcription takes time. In addition, the basal cells **proliferate** to make that epidermis taller. Proliferation offers the opportunity for mutations, which is why **sun exposure**, even without sunburns, increases risk of squamous cell and basal cell carcinoma.

If the epidermis is removed from UV exposure, the basal cells go back to their default signaling, the proliferation ends, and the excess melanosome synthesis returns to the default. **Tanning fades without chronic exposure.**

Chronic exposure without sunburns induces **melanocyte proliferation**. Medical science knows that melanocyte density increases after chronic UV exposure, and that it takes about a week to start and the increased number of melanocytes is seen at 14 days. Melanocytes are terminally differentiated and are very stable cells—they do not proliferate under normal conditions. But with UVB exposure, they do proliferate. Proliferation increases the risk of mutations. UV exposure can cause accumulation of DNA mutations. In particular, **BRAF** and **RAS** are extremely consequential for lesions of melanocyte proliferation.

Linear melanocyte hyperplasia is termed **lentiginous hyperplasia**, and is seen in lentigo (below). No mutations are seen in melanocytes of lentigo disorders. Nonlinear melanocyte hyperplasia, aka **melanocyte nests**, is seen in both noncancerous nevi (moles) and melanoma. Nested proliferation is a result of DNA damage. BRAF or RAS are mutated and the melanocyte begins proliferating. The melanocytes form nests and move from the epidermis to the dermis. In moles, no additional mutations are accumulated, and the unregulated melanocyte proliferation ends with the senescent, almost scarred nests in the dermis. Moles, therefore, do not continue to grow. In melanoma, additional mutations are accumulated, the unregulated melanocyte proliferation does not stop, mitosis is vigorous, and the nests continue to expand and metastasize.

Melanocyte proliferation leads to moles and melanoma. However, throughout a human's life, melanocyte stem cells are supposed to proliferate in order to sustain the population of healthy melanocytes. They divide and differentiate a daughter to a melanocyte. Like all stem cells, melanocyte stem cells have a limited number of divisions before they become senescent. **Greying** of hair is a product of melanocyte stem cells running out of divisions. As a person ages, the stem cell population becomes senescent. As more stem cells burn out of divisions, the skin tone lightens, the hair greys, and patients become more vulnerable to UV radiation.

Disorders of pigmentation are disorders of melanocytes. Where normal skin pigmentation is dependent on biochemical activity of keratinocytes, abnormal skin pigmentation can be from activity, production, or hyperplasia of melanocytes. We'll cover each disease one at a time.

Diseases of Hypopigmentation

The two diseases of hypopigmentation that are board relevant are vitiligo and albinism. Vitiligo results from the autoimmune destruction of melanocytes. This destruction occurs in noncontiguous patches—some are lost, but those that remain function normally. Albinism results from a genetic deficiency of a protein required for the synthesis of melanin—the number of melanocytes remains the same, but the production of pigment is compromised globally.

Vitiligo. Vitiligo is a disease of **hypopigmentation**. Vitiligo is caused by the **autoimmune destruction of melanocytes**, leading to a loss of melanin pigment in the epidermis. The autoimmune mechanism is not well understood. Most easily seen on patients with dark skin, there is a complete loss of pigment in affected areas. The areas affected are **irregular** macules (small patches) or patches (large macules) of **complete depigmentation**. These regions of complete depigmentation are **asymptomatic** and lack any signs of inflammation. These lesions can appear at any age and anywhere on the body, but are common on **extensor surfaces** and **around body orifices**. Vitiligo is frequently associated with **autoimmune thyroid disease** (Hashimoto's more than Graves'). That link doesn't make immediate logical sense, making it great board fodder.

Albinism. Albinism is an **autosomal recessive** genetic disorder of **melanin synthesis**. The genetic defect causes a deficiency of **tyrosinase**, which transforms DOPA into melanin (a more moderate form is from a defective tyrosine transport). Without the ability to synthesize melanin, melanocytes have no pigment to distribute. Which means there is a **normal melanocyte count**, but with **decreased melanin production**. This is genetic, so affects all melanocytes in every tissue. There is **hypopigmentation** of the **skin**, **hair**, and **iris**, sometimes so severe that vision is compromised.

DISEASE	NOTES
Vitiligo	Autoimmune destruction of melanocytes Irregular areas of complete depigmentation, patches on extensor surfaces Asymptomatic Associated with thyroid disease
Albinism	Autosomal recessive disorder of melanin biosynthesis (tyrosinase deficiency) Normal melanocyte number with decreased biosynthesis Affects entire body, all hypopigmented—skin, hair, iris; possible vision impairment High risk for all skin cancers

Table 5.1: Diseases of Hypopigmentation
This table is meant to summarize, not compare the two diseases.

Disorders of Hyperpigmentation

Freckles. Freckles are called ephelides (singular ephelis) and represent a normal epidermis and **normal number of melanocytes**, but with **large melanosomes**. Freckles are associated with a variety of M1CR gene mutations. None of them is causative, but it is not surprising to find that the signal for more pigment is activated, not more melanocytes. Ephelides are benign skin lesions that are usually round in shape, light to dark brown in color, and are just a few millimeters in diameter. They are **well-demarcated hyperpigmented macules** occurring in fair-haired individuals—redheads and blondes. These lesions **do respond to sunlight**, so will be larger in size and number during summer months and smaller and lighter in winter months. Since they are UV sensitive, they will occur on sun-exposed areas, and will **fade in the absence of sun exposure**. Freckles should be diagnosed in a young fair-haired person.

Simple lentigo. A simple lentigo (plural lentigines) is a dark brown macule (darker and larger than an ephelis) that can occur at any age, though is often initiated in infancy. More may develop during childhood and puberty. Although flat and dark, a lentigo is **not** induced by sun exposure, and so will occur on any region of skin, and will not darken with UV light. They are found on all tones of skin. The histologic appearance is a **linear (non-nested) melanocytic hyperplasia** restricted to the cell layer immediately above the basement membrane. If you think "freckle" but then it "doesn't change with sunlight," it is likely a simple lentigo. These are dark "birth" marks.

Solar lentigo. A solar lentigo, commonly referred to as a sun spot or liver spot, represents another non-nested, linear hyperplasia of melanocytes, but with **increased activity** of melanocytes, leading to **hyperpigmentation** of the stratum basale. These are **hyperpigmented macules** (or patches) of the **elderly**. They are usually tan or dark brown, have irregular borders, and may become quite large. They are induced by UV light, so will occur on **sun-exposed areas**. Whereas freckles are induced by UV light, then fade, and are found on younger patients, solar lentigines are induced by **cumulative UV light**, so do not fade, and are found on the elderly.

Lentigines, histologically, means linear hyperplasia of melanocytes.

Melanotic Nevi (Moles)

Moles are also a disorder of hyperpigmentation. But there is enough to learn about them that they warrant their own section. Moles are one step closer to melanoma. Whereas the hyperpigmented lesions that came before were either more active melanosomes (ephelis) or non-nested hyperplasia of melanocytes (lentigo), moles, like their malignant cousin melanoma, are caused by **nested hyperplasia of melanocytes**.

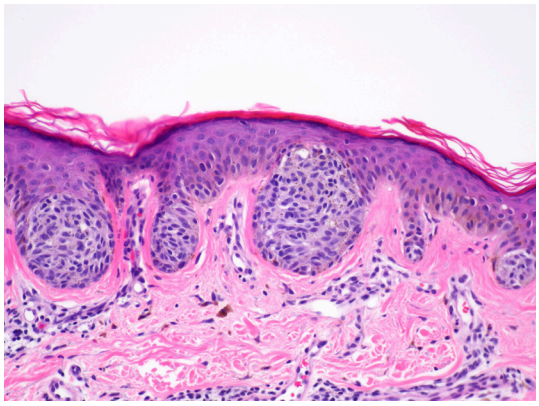
Moles are called **melanotic nevi** and represent a **benign proliferation of melanocytes**. Moles can be macular (flat) or papular (raised). Melanocytes don't tend to hang out together—they have their dendrites to handle a wide area of basal cells. But when they do proliferate, they form **nests**. The location of those nests nest will determine the type of acquired nevus. The presence of nests indicates abnormal behavior of melanocytes. Nests do NOT necessarily mean cancer (though their histologic appearance can be similar).

Moles can be congenital or acquired. **Congenital nevi** are present at **birth** or within the first few months of life. These are benign lesions but do have the potential to transform into melanoma. The risk of melanoma transformation is correlated to the size of the nevus. Bigger nevi have greater risk.

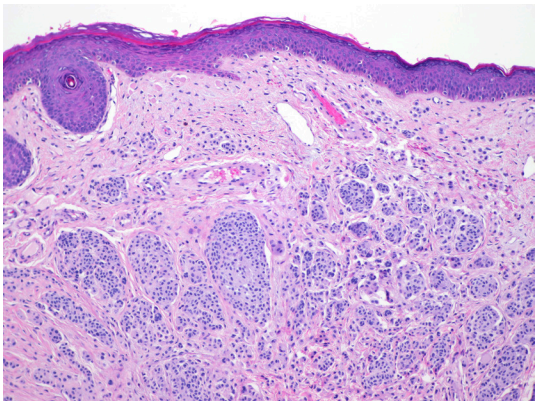
Acquired nevi are induced by sun exposure (UV damage), and so develop in **sun-exposed areas**. Some of the same genetic changes of melanoma have been found in moles—BRAF kinase overactivity, for example—but do not acquire other traits of malignancy. Moles stop growing because of oncogene-induced senescence. A new melanotic lesion could be cancer, or just a mole. You should think of it this way: when the UV damage happens, the melanocyte changes. It either changes into malignancy or it changes into a mole. You don't know which one it is when the UV damage hits. The only way you can know is by monitoring over time. If it progresses to show ABCDE, then that UV damage was enough to make it go malignant. If it doesn't ever progress to ABCDE, then that UV damage only made it a mole.

All melanotic nevi progress through these morphologic changes over time. The earliest lesions are **junctional nevi**, which consist of nests of round cells that are uniform and rounded in contour, appearing at the dermal-epidermal junction. These moles are new and close to the surface, so generally appear flat and dark black. This is where melanocytes begin, and where the melanocytes of nevi begin proliferating. As they proliferate (and this is going to sound an awful lot like invasion, but it isn't), the nests break through the basement membrane, forming a **compound nevus**—the same cells and mitosis of a junctional, just with nests on either side of the basement membrane. Eventually, these nests will evolve or cords of melanocytes in the dermis only, where they are referred to as **dermal nevi**. These nests are deeper, so their pigment is farther from the surface, so they are brown or tan colored. They are deeper, so have to push harder to the surface, thus they appear as papules.

"Nests of melanocytes in the dermis" defines melanoma, the nests having invaded through the basement membrane. To a dermatopathologist, a slide of melanoma is obviously different from a slide of a nonmalignant dermal nevus. As a student, it might not be so easy. Here's the thing, though. When the mole first starts developing, the melanocytes are young and fresh. That means they are large, produce a lot of melanin, grow in nests, and are mitotically active. Because these cells do not become immortalized, the more they replicate, the closer to senescence they get. The dermal lesions are late lesions, after the melanocytes have replicated many times. The deepest melanocytes are the senescent melanocytes, which appear smaller, produce little to no pigment, are not mitotically active, and may lose these nests in favor of cords or individual cells. This correlates to a gross loss of tyrosinase activity. Melanoma retains all melanocyte properties and grows in monstrously sized nests below the basement membrane. A **dysplastic nevus** is made of melanocytes that have acquired the mutations necessary to fuel malignancy, but in which the complete transition has not occurred. You may be asked to recognize a clearly nondysplastic dermal nest from a clearly malignant dermal nest; you will not be asked to distinguish a dysplastic nevus from either.



(a)



(b)

Figure 5.2: Moles
(a) Junctional melanocytic nevus is characterized by nests of benign melanocytes along the basal layer of the epidermis (i.e.—at the "junction" between the epidermis and dermis (c) Intradermal melanocytic nevus is characterized by nests of benign melanocytes in the dermis.

CONDITION	NOTES
Freckles (ephelides)	Macules that get darker and increase in number with UV exposure Normal number of melanocytes, increased melanosomes Fair-haired, fair-skinned
Simple lentigo	Macules that do NOT change in size or number with UV exposure A freckle that doesn't fade
Solar lentigo	Hyperpigmented macules (or patches) of the elderly Cumulative UV damage, normal melanocytes, normal melanosomes
Junctional nevus	Nests are above the basement membrane in the epidermis Melanocytes are large, mitotically active, producing pigment Nests are closer to surface, so appear raised (papules), and darker (black)
Compound nevus	Nests are on both sides of the basement membrane Melanocytes are large, mitotically active, producing pigment, but less than junctional Have the average appearance, slightly raised (papules), and a mixed color (brown)
Intradermal nevus	Nests are under the epidermis in the dermis Melanocytes are small, mitotically inactive, produce little pigment, and have small nests Nests are farther from surface, so appear flatter (macules) and lighter (tan)

Table 5.2: Hyperpigmented Marks

Citations

Figures 5.1b, 5.2a, 5.2b: Courtesy of Jerad M. Gardner, MD.